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PET and PET/CT for Monitoring Response to Cancer Therapy

By Rodney J. Hicks, M.D.

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Discuss the limitations of conventional structural imaging techniques for evaluating response to cancer treatments.
- Explain the advantages and limitations of metabolic response evaluation using FDG-PET.
- List the varying methodologies used to define metabolic response.
- Recognize the limitations of FDG-PET for evaluating therapeutic response and describe approaches that may be helpful in addressing these pitfalls.

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Dr. Hicks has no significant financial arrangement or affiliation with any manufacturer of any pharmaceutical or medical device and is not affiliated in any manner with any provider of any commercial medical or healthcare professional service.

PET is increasingly being used to evaluate patients with known or suspected cancer at all phases of the diagnostic process. The role of PET as a technique for therapeutic monitoring is expanding rapidly. Earlier and more robust identification of nonresponders could prove cost-saving if it leads to the earlier termination of ineffective treatment. It would also have important benefits to the individual patient by allowing an earlier change to alternative treatments that may be more efficacious or by avoiding the unnecessary toxicity of ineffective therapy. Conversely, lack of apparent morphologic response may belie important biologic effects, leading to cessation of effective therapies.

Most studies performed for therapeutic monitoring use the glucose analog fluorine-18 fluorodeoxyglucose (FDG), although new radiopharmaceutical tracers may also prove useful in this application.

Monitoring response to cancer therapy has two important roles. First, it helps the managing clinician determine the need for ongoing treatment and its nature in an individual patient. Second, it is often used as an end point to determine the efficacy of a cancer therapy in clinical trials. The latter role relies on the demonstration that imaging results can act as surrogates for measures of survival.

Conventional assessment of therapeutic response relies on changes in the dimensions of structural lesions based on CT, ultrasound, x-ray, or MR imaging. These changes are codified in the RECIST (Response Evaluation Criteria in Solid Tumors) criteria.¹ Changes in lesion size are relatively slow to occur,

however, particularly when there is a preexisting necrotic or fibrotic component within cancer lesions. Furthermore, some disease processes heal by fibrosis, leaving a significant residual mass and limiting the

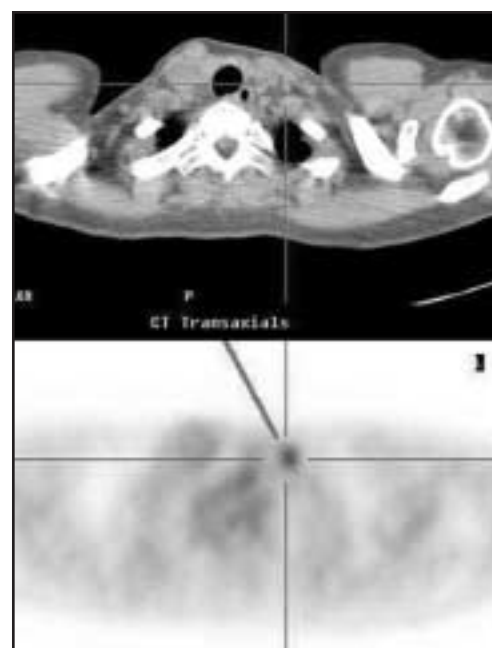


Figure 1. Following completion of chemotherapy for a locally advanced carcinoma of the left breast, a complete response was recorded on CT, but FDG-PET demonstrated multiple foci of uptake in the left axilla and supraclavicular fossa. Biopsy of the nonenlarged lymph node shown on CT (top) that had moderate FDG uptake on PET (bottom) confirmed residual disease.

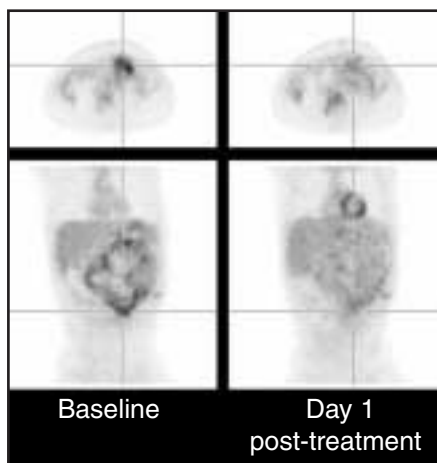


Figure 2. Representative coregistered FDG-PET images in transaxial (top) and coronal (bottom) planes of a patient with a large centrally necrotic gastrointestinal stromal tumor at baseline (left) and 24 hours after commencing imatinib (Glivec). Hypermetabolic rim of tumor had marked reduction in uptake. Patient derived symptomatic benefit but had no radiologic response, with a stable residual mass corresponding to the central photopenic central region on the baseline study.

ability to confirm a complete response.

Secondary fibrotic changes in soft tissues adjacent to tumor sites as a result of radiotherapy or surgery can also complicate evaluation of response to cancer therapies. These factors may lead to continuation of treatment for longer than necessary or to a change in therapy that may not be required in the case of lesions that have responded well to treatment. On the other hand, structures such as lymph nodes that return to normal size may still harbor disease, and, hence, partial responses can appear to be complete. This may result in premature cessation of treatment (Figure 1).

The fact that metabolic changes tend to

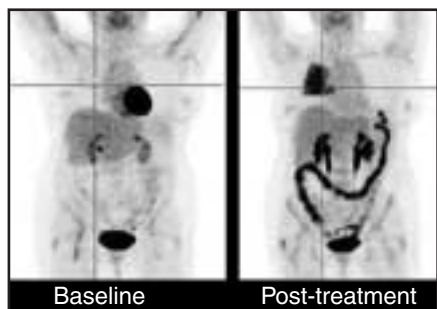


Figure 3. Maximum intensity projection (MIP) images of the baseline FDG-PET study (left) demonstrate focal uptake in the right midzone related to a right upper lobe lung cancer. Following radiotherapy, progressive CT abnormality suggested a poor response to treatment. Post-treatment MIP demonstrates a geographic distribution of abnormality, indicating active pneumonitis. The SUV in the involved lung was higher than that recorded for the primary tumor, demonstrating the limitations of relying purely on semiquantitative measures.

occur more rapidly than regression of structural changes provides a major theoretical advantage for PET over structural imaging techniques. One of the most dramatic examples is the rapid reduction of FDG uptake in gastrointestinal stromal tumors following treatment with an agent that blocks the c-kit oncogene product.² Metabolic responses can be apparent within 48 hours of beginning treatment (Figure 2).

A large body of evidence suggests that an early or marked reduction in the uptake of FDG by a range of tumors with high initial avidity is predictive of subsequent morphologic response. Preliminary studies reported more than 10 years ago demonstrated that reduced FDG uptake in breast cancer preceded and predicted morphologic response to chemohormonotherapy.³ Numerous other studies since then have demonstrated that reduction in FDG uptake correlates with subsequent clinical and radiologic response. These results have led to recommendations for wider use of FDG-PET in therapeutic response assessment and attempts to codify response categories.⁴

METABOLIC RESPONSE

The term “metabolic response” usually denotes a qualitative or measured reduction in FDG uptake in tumoral sites. Various authors have used post hoc determination of the percentage reduction in the quantitative and semiquantitative measures of FDG uptake to optimize the predictive accuracy of FDG-PET for subsequent therapeutic response. The criteria for dichotomizing patients into responders and non-responders have varied considerably in the percentage reduction in the measured parameter and have involved marked differences in the timing of the response assessment during or after therapy. In an attempt to achieve a consensus position, the European Organization for Research and Treatment of Cancer previously promulgated guidelines for the methodology of performing serial FDG-PET evaluations and reporting metabolic response.⁴ Attempts to simplify the process of metabolic response assessment have tended to trivialize the complexity of the issues involved.

While a reduction in FDG uptake in lesions is usually seen in responding lesions, a transient increase, or “metabolic flare,” may be predictive in some situations of subsequent clinical benefit. This has recently been described in the setting of tamoxifen in metastatic breast cancer.⁵ An increase in FDG uptake in this case may reflect a partial agonist effect of the treatment drug on estrogen receptor-positive cells or increased energy utilization related to induction of apoptotic pathways.

In vitro data suggest that a transient increase in FDG uptake can also occur following exposure of cells to radiation.⁶ This may, in part, explain the imperfect negative predictive value of early FDG-PET in evaluating the likelihood of subsequent clinical response to external-beam radiotherapy, although an inflammatory response has been postulated to be the major cause.⁷ Inflammatory responses to therapeutic interventions may limit the ability of PET to assess response. False-positive results related to persisting metabolic signal from white cell infiltration obscuring a favorable metabolic response in tumoral elements has been seen as a significant limitation of routine application of FDG-PET in therapeutic monitoring.⁸ However, recognition of differences in the patterns of uptake abnormality that occur in inflammatory and malignant processes (Figure 3) can help minimize the impact of these putative false-positive results.⁹

CLASSIFICATION

One of the major issues that must be considered in using PET for cancer therapy response assessment is the methodology by which metabolic responses are classified. While a complete metabolic response, representing normalization of the PET scan appearance, is likely to be fairly consistently interpreted among reporting physicians and institutions, the methodology used to define an incomplete metabolic response is less clearly defined. Methods used vary in complexity from simple qualitative comparison of baseline and post-treatment scans to fully quantitative evaluation approaches involving arterial blood sampling, prolonged dynamic imaging, and complex compartmental modeling.

Despite its simplicity, the subjectivity of qualitative reporting has been seen as a limitation. As with any qualitative analysis of digital data, consistent display of the PET images is critical if reproducible results are to be obtained. Just as it would be inappropriate to evaluate a lung lesion on one occasion using lung windows and on another using mediastinal soft-tissue windows, it is also inappropriate to use inconsistent thresholding of PET images. One approach to standardization is to display the baseline and post-treatment scans on a scale based on the standardized uptake value. The SUV is a parameter that corrects measured radioactive counts in a given tissue, calibrated against a known amount of radioactivity, for the amount of radioactivity administered, radioactive decay, and the size of the individual.¹⁰

An alternative to using an SUV-calibrated scale is to normalize the two sets of images so that the intensity of a reference tissue on each scan is the same on a selected gray or color scale.

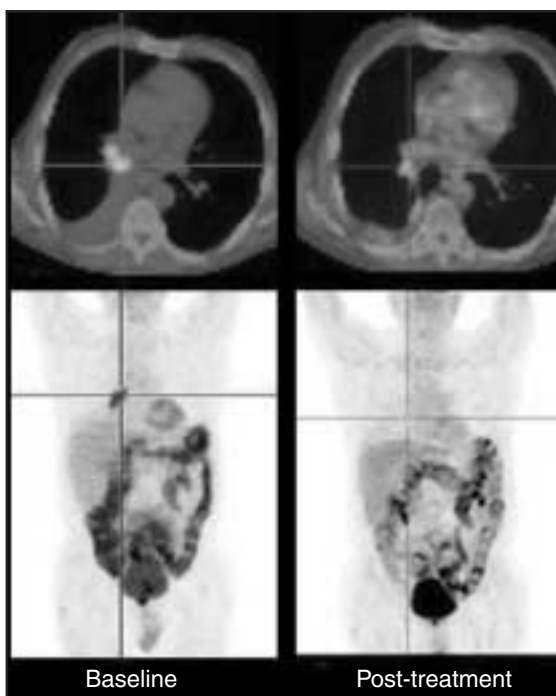


Figure 4. On baseline PET/CT scanning (top left) peripheral collapse beyond the primary tumor is clearly differentiated from the primary and an adjacent node by the intensity of FDG-PET abnormality (bottom left). Complete radiologic response is seen following treatment with chemoradiation (top right), but PET demonstrates ongoing low-grade FDG uptake in the primary, suggesting a partial metabolic response (bottom right). Normalization of each image set to hepatic activity allows qualitative comparison of the baseline and post-treatment scans.

This can be done using visual cues or software techniques. We normalize coregistered baseline and follow-up FDG-PET scans using the liver as the reference tissue, reasoning that, apart from the brain and, variably, the heart, hepatic tissue has the highest normal soft-tissue uptake of FDG under fasting conditions.

Using a linear gray scale, the liver is set in the middle of the 256-level gray scale (midgray) (Figure 4). For fused PET/CT images, we use a rainbow color scale for the PET data with the liver set at the interface between blue and green. With these guidelines, the intensity of tissues, such as mediastinal blood pool, and bone marrow can be reproducibly compared with hepatic activity, and the relative intensity of tumor deposits can be appreciated between studies.

In our facility, we have developed and use a standardized nomenclature for qualitative reporting of serial FDG-PET scans in therapeutic monitoring that can be applied to all tumor types. In our schema, a complete metabolic response (CMR) is defined as a return of FDG uptake in previously documented lesions to a level equivalent to or less than residual radioactivity in normal tissues within the organ in question. A partial metabolic response (PMR) constitutes a significant reduction in FDG

uptake in tumor sites based on visual inspection of appropriately displayed comparative images. Stable metabolic disease and progressive metabolic disease are defined, respectively, by a lack of change or an increase in the intensity and extent of metabolic abnormality in a pattern consistent with tumor growth.

We have reported that powerful prognostic stratification is provided using this schema for the evaluation of therapeutic response to radical radiotherapy in patients with non-small cell lung cancer.¹¹ The frequency and prognostic value of a CMR are likely to be influenced by the responsiveness of the tumor to treatment, the biologic aggressiveness of the disease process, and the timing of the follow-up scan after treatment. While patients with a CMR will not necessarily be cured, it is likely that most patients who do achieve a durable remission of cancer will come from this group. Supporting this, the prognostic value of a CMR on FDG-PET after completion of chemotherapy has also been demonstrated in lymphoma.¹²

The earlier FDG-PET scanning is performed during therapy, the lower the likelihood that the metabolic signal from remaining viable cancer cells will reduce to a level where it is undetectable or that qualitative progression will have occurred. Therefore, PMR or stable disease has predominated in many FDG-PET therapeutic monitoring trials, particularly those involving chemotherapy. Where abnormal radiotracer uptake remains in a lesion, determination of the degree to which it has reduced may have therapeutic and prognostic implications. In such cases, measurement of lesion radiotracer uptake may provide a more objective evaluation than qualitative assessment.

FDG uptake can be measured in tumor sites by a number of techniques. They vary in complexity and reproducibility and, as yet, no consensus exists on the most appropriate method. Using the exquisite sensitivity of PET to measure radioactivity in both the blood and tissue over time has enabled development of tracer kinetic models that correlate well with known biochemical processes, providing unique insights into the mechanism of many diseases.¹³ But tracer kinetic modeling involves assumptions that may not necessarily be valid in cancer cells¹⁴ and is a technically and computationally

complex technique that is not easily implemented in clinical practice.

For cancer, however, the major impediment to routine application of quantitative measure of glucose metabolic rates is the need to perform dynamic imaging over an hour or so in a single bed position, limiting evaluation to 10 to 25 cm of the body, depending on the axial field of the scanner. This negates the whole-body screening advantages of modern PET scanners or necessitates an additional whole-body study after completion of the dynamic scan, which substantially decreases throughput of patients and increases the cost of PET.

Furthermore, where differential responses may occur in various tumor sites, it is not possible to prospectively identify which target lesion might be best for quantitative evaluation. Nevertheless, numerous studies using quantitative measurement of glucose metabolic response have demonstrated that FDG-PET performed early in therapy can predict subsequent morphologic response. More practical methods are the use of serial SUV calculations or tumor-to-background ratios, as these can be applied to whole-body imaging studies. Again, numerous studies demonstrate that a reduction in these semiquantitative parameters is predictive of a subsequent morphologic response.⁴

CLINICAL SIGNIFICANCE

Recognizing the significant limitations of morphologic imaging in assessing therapeutic response, the demonstration that an early FDG reduction correlates well with subsequent reduction in tumor dimensions is, however, not sufficient to validate PET as a therapeutic monitoring tool. Many authors have therefore

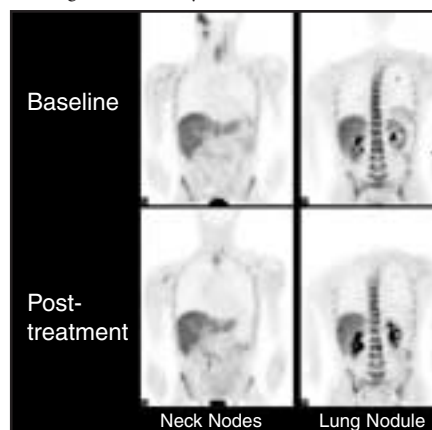


Figure 5. FLT images at baseline demonstrate high uptake in extensive left cervical lymphadenopathy (top left) and in a lung nodule (top right) as well as in bone marrow, related to hematopoietic cell proliferation. Two weeks following treatment, no FLT uptake was detectable in the neck nodes and a significant reduction in uptake in the lung nodule was seen. Progressive lung disease was subsequently confirmed.

sought to validate metabolic response by comparison with subsequent evaluation of pathologic response. While this may appear to be an objective method of validation, it is pertinent only to those patients who undergo surgery or biopsy, and it may be subject to sampling error.

Since many patients now receive chemotherapy or radiotherapy alone or in combination as part or all of their cancer therapy, pathologic validation of therapeutic response is often not available. This poses significant problems for the evaluation of the clinical efficacy of PET as a therapeutic monitoring tool.¹⁵ And the presence of apparently viable cells in a pathologic specimen after treatment with radiotherapy does not necessarily indicate that these cells have long-term clonogenic potential. Accordingly, it is likely that PET will be a worthwhile technique for therapy response monitoring only if it provides a more robust and practical surrogate for outcomes, such as progression-free or overall survival. More studies evaluating the prognostic significance of metabolic response results are required.

POTENTIAL ADVANTAGES OF PET/CT

The whole-body screening capability of PET makes discordant responses readily apparent. In addition, PET is not limited to "measur-

able" lesions in the way that CT and MR are. Issues of bioavailability of drugs in different tissues and development of clonal heterogeneity due to the intrinsic genomic instability could lead to differential therapeutic response in different lesions in a given individual. By demonstrating this, PET, particularly when performed on a current-generation combined PET/CT scanner, allows metabolically guided biopsy.¹⁶ By revealing the presence of significant nonviable components prior to treatment, PET/CT should improve assessment of the reduction in disease bulk with neoadjuvant therapies. The marrying of structural and functional information should also allow superior sensitivity for residual small-volume disease by allowing corrections for partial volume effects.

ALTERNATIVE TRACERS

PET tracers that demonstrate an increased rate of cellular proliferation are likely to be particularly helpful in the setting of therapeutic monitoring, because they are less likely to be taken up in inflammatory conditions. The search for proliferation markers has been active, with most attention to thymidine analogs. Although carbon-11 thymidine has been synthesized and used to evaluate the proliferative rate of tumors, its short physical half-life and the metabolic degradation of the radiotracer limits its clinical application.

To date, the most promising proliferation tracer for clinical application appears to be fluorine-18 fluorothymidine (FLT).^{17,18} Automated synthesis units are now commercially available for this agent. There is good evidence that FLT uptake is closely correlated with cellular proliferation, with correlation between the intensity of uptake as measured by SUV with proliferation indices such as Ki-67 staining in suspected lung cancer lesions undergoing resection.¹⁹ FLT is thus an exciting tracer for therapeutic monitoring, especially for therapies that may have a tumorigenic rather than tumoricidal mode of action (Figure 5).

CONCLUSION

PET is already an important technique for the assessment of therapeutic response in centers where it is available. Improvements in methodology, wider availability, and better tracers will likely increase the proportion of studies that are performed for the purpose of determining ongoing treatment strategies. Awareness is also growing of PET's potential to provide a clearer idea of the relative efficacies of competing therapies well before such information could be obtained from conventional therapeutic trials. Accordingly, the pharmaceutical industry and regulators are developing strategies for incorporating PET into drug development.

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